

Answer 1:

Bibliographic Information

Potential of 2-chlorodeoxyadenosine activity by bryostatin 1 in the resistant chronic lymphocytic leukemia cell line (WSU-CLL). Association with increased ratios of dCK/5'-NT and Bax/Bcl-2. Mohammad, Ramzi M.; Beck, Frances W. J.; Katato, Khalil; Hamdy, Nayera; Wall, Nathan; Al-Katib, Ayad. Department Medicine, Division Hematology Oncology, Karmanos Cancer Institute, School Medicine, Wayne State University, Detroit, MI, USA. Biological Chemistry (1998), 379(10), 1253-1261. Publisher: Walter de Gruyter & Co., CODEN: BICHF3 ISSN: 1431-6730. Journal written in English. CAN 129:270219 AN 1998:685786 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The activities of 2-chlorodeoxyadenosine (2-CdA) metabolizing enzymes, deoxycytidine kinase (dCK) and cytosolic 5'-nucleotidase (5'-NT) were measured in bryostatin 1 treated chronic lymphocytic leukemia (CLL) cells using an EBV-neg. WSU-CLL cell line. This cell line was established from a patient with CLL resistant to fludarabine. The results revealed an increase in dCK activity in bryostatin 1 treated cells at 48 and 72 h compared with the control. 5'-NT activity decreased at 48 h. The ratio of dCK to 5'-NT activity was increased in bryostatin 1 treated WSU-CLL cells after 48 h. WSU-CLL cells treated with bryostatin 1 exhibited an increase in the % of apoptotic and dead cells from control levels of 16% to 40%. This % was further increased to 67% following the addn. of 11.2 μ M 2-CdA to WSU-CLL cells pretreated with bryostatin 1. Results from Western blot indicate that WSU-CLL cells express high levels of Bcl-2, Bcl-xL, and c-myc, and a low level of Bax. P53 in untreated WSU-CLL cells is undetectable. WSU-CLL cells treated with bryostatin 1 showed an increase in the ratio of Bax:Bcl-2. To demonstrate that the bryostatin 1 mediated enhancement of 2-CdA efficacy was not restricted to in vitro cell culture, the authors have studied the tumor growth delay of WSU-CLL xenografts treated with placebo, bryostatin 1, 2-CdA, and bryostatin 1 followed by 2-CdA. SCID mice given bryostatin 1 at 75 μ g \times kg⁻¹ \times d⁻¹ for 5 days followed by 30 mg \times kg⁻¹ \times d⁻¹ 2-CdA for 5 days in 2 cycles, had improved tumor growth delay. The authors conclude that bryostatin 1 is not only capable of inducing apoptosis by itself, but also sensitizes de novo resistant WSU-CLL cells to the chemotherapeutic effects of 2-CdA. The bryostatin 1 induced increased ratio of dCK/5'-NT activity and an increased ratio of Bax/Bcl-2 are at least 2 mechanisms through which this natural compd. is able to potentiate the antitumor activity of 2-CdA in otherwise resistant CLL cells.

Answer 2:

Bibliographic Information

Sequential treatment of human chronic lymphocytic leukemia with bryostatin 1 followed by 2-chlorodeoxyadenosine: preclinical studies. Mohammad, Ramzi M.; Katato, Khalil; Almatchy, Victor P.; Wall, Nathan; Liu, Kan-Zhi; Schultz, Christian P.; Mantsch, Henry H.; Varterasian, Mary; Al-Katib, Ayad M. Division of Hematology and Oncology, Karmanos Cancer Institute, Department of Medicine, Wayne State University School of Medicine, Detroit, MI, USA. Clinical Cancer Research (1998), 4(2), 445-453. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 128:239082 AN 1998:130543 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors have previously reported that bryostatin 1 (Bryo 1) induces differentiation of chronic lymphocytic leukemia (CLL) in vitro to a hairy cell (HC) stage. This study tests the hypothesis that Bryo 1-differentiated CLL cells are more susceptible to 2-chlorodeoxyadenosine (2-CdA) than parent CLL cells. A recently established EBV-neg. CLL line (WSU-CLL) from a patient resistant to chemotherapy including fludarabine was used to test this hypothesis. Both Bryo 1 (10-1000 nM) and 2-CdA (5.6-22.4 μ M) exhibited a dose-dependent growth inhibitory effect on the WSU-CLL cell line. In vitro, the sequential exposure to Bryo 1 (100 nM for 72 h) followed by 2-CdA (11.2 μ M) resulted in significantly higher rates of growth inhibition than either agent alone. Changes in immunophenotype, enzymes, lipids, proteins, and the DNA of WSU-CLL cells were studied before and after Bryo 1 treatment. Bryo 1 induced a pos. tartrate-resistant acid phosphatase reaction and two important markers, CD11c and CD25, after 72 h of culture, confirming the differentiation of CLL to HC. The Fourier transformation IR spectroscopic anal. showed that the amt. of membrane lipids significantly increased in Bryo 1-treated cells compared to controls after 24 h, whereas the protein content, as well as the DNA content, decreased. This finding supports the change of CLL to HC. To evaluate the in vivo efficacy of Bryo 1 and 2-CdA, the

authors used a xenograft model of CLL in WSU-CLL-bearing mice with severe combined immune deficiency. S.c. tumors were developed by injection of 107 WSU-CLL cells, and fragments were then transplanted into a new batch of severe combined immunodeficient mice. Bryo 1 and 2-CdA at the max. tolerated doses (75 µg/kg i.p. and 30 mg/kg s.c., resp.) were administered to the mice at different combinations and schedules.

The survival in days, the tumor growth inhibition ratio, the tumor growth delay, and the log₁₀ kill of the mice treated with Bryo 1 followed by 2-CdA were significantly better than the control and other groups. The authors conclude that the sequential treatment with Bryo 1 followed by 2-CdA resulted in higher antitumor activity and improved animal survival.

Answer 3:

Bibliographic Information

Development and molecular characterization of a 2',2'-difluorodeoxycytidine-resistant variant of the human ovarian carcinoma cell line A2780. Ruiz van Haperen, Veronique W. T.; Veerman, Gijsbert; Eriksson, Staffan; Boven, Epie; Stegmann, Alexander P. A.; Hermesen, Mario; Vermorken, Jan B.; Pinedo, Herbert M.; Peters, Godefridus J. Dep. Oncol., Free Univ. Hosp., Amsterdam, Neth. Cancer Research (1994), 54(15), 4138-43. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 121:148492 AN 1994:548492 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

2',2'-Difluorodeoxycytidine (gemcitabine, dFdCyd) is a deoxycytidine analog with promising antitumor activity. In order to be active it must be phosphorylated by deoxycytidine kinase (dCK). The authors induced resistance to dFdCyd in the human ovarian carcinoma cell line A2780 by exposure to increasing concns. of dFdCyd. The IC₅₀, defined as the concn. of dFdCyd causing 50% growth inhibition, at 72 h exposure increased from 0.6 nM dFdCyd in A2780 to 92 µM in the resistant variant, named AG6000. Although the resistant cell line is routinely cultured in 6 µM dFdCyd, the resistant phenotype can be maintained for at least 10 passages without dFdCyd. AG6000 is cross-resistant to other drugs which require activation by dCK, such as 1-β-D-arabinofuranosylcytosine, 5-aza-2'-deoxycytidine, and 2-chlorodeoxyadenosine. There was no specific dCK activity in exts. from AG6000 cells. Western blot anal. using a polyclonal anti-dCK antibody did not reveal any dCK protein in AG6000 cell exts. Reverse-transcribed and PCR-amplified mRNA, using specific dCK primers, demonstrated that AG6000 expressed a normal length amplicon of 701 base pairs, besides an aberrant amplicon of 500 base pairs. Chromosome spreads from the cell lines showed no major differences between A2780 and AG6000. The latter cell line was also cross-resistant to 2',2'-difluorodeoxyuridine, the deamination product of dFdCyd. Addnl., cross-resistance to the multidrug resistance drugs doxorubicin and vincristine was obsd. This was not assocd. with the induction of P-glycoprotein, as detd. by the RNase protection assay. Injection of AG6000 cells s.c. into nude mice demonstrated that the cell line had retained its tumorigenicity; AG6000 xenografts were not sensitive to dFdCyd treatment, in contrast to the parental A2780 tumors. No dFdCyd triphosphate accumulation was found in the resistant tumors, in contrast to the parental A2780 tumors. These results indicate that the dFdCyd resistance phenotype is stable, and mainly due to dCK deficiency.

Answer 4:

Bibliographic Information

Antitumor activity of 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine, a novel deoxyadenosine analog, against human colon tumor xenografts by oral administration. Takahashi T; Kanazawa J; Akinaga S; Tamaoki T; Okabe M Cancer Chemotherapy, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co. Ltd., Japan Cancer chemotherapy and pharmacology (1999), 43(3), 233-40. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9923554 AN 1999120429 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

2-Chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl) adenine (Cl-F-araA) is a novel deoxyadenosine analog, which inhibits DNA synthesis by inhibiting DNA polymerase alpha and ribonucleotide reductase. Cl-F-araA shows potent

antiproliferative activity against several leukemic cell lines including those of human origin and is also effective against murine solid tumors, in particular being curative against colon tumors. **PURPOSE:** We therefore decided to investigate whether CI-F-araA is effective against human colon tumors, in particular by oral administration, since it has improved stability compared with other deoxyadenosine analogs. **METHODS:** Antiproliferative activity in vitro was determined from cell counts. Subcutaneously inoculated xenograft models and a liver micrometastases model were used for assessment of antitumor activity in vivo. **RESULTS:** CI-F-araA showed potent antiproliferative activity against four human colon tumor cell lines (HCT116, HT-29, DLD-1, WiDr), with a 50% growth-inhibitory concentration (IC₅₀) of 0.26 microM with a 72-h exposure. This activity was greater than those of fludarabine desphosphate and cladribine, other deoxyadenosine analogs, which showed IC₅₀ values of 19 microM and 0.35 microM, respectively. CI-F-araA showed potent antitumor activity against four human colon tumor xenograft models (HT-29, WiDr, Co-3, COLO-320DM) in a 5-day daily administration schedule, which was shown to be the most effective of three administration regimens tested (single, twice-weekly, 5-day daily). In particular, oral administration showed significantly superior activity, with a regressive or cytostatic growth curve, compared with intravenous administration. In addition, CI-F-araA was effective at only one-sixteenth of the maximum dose tested in a 10-day daily administration schedule. Therapeutic efficiency seemed to increase in proportion to the frequency of administration.

CI-F-araA also decreased liver micrometastases created by intrasplenic injection of human colon tumor cells, leading to complete suppression at the maximum dose tested. **CONCLUSIONS:** These results suggest that CI-F-araA might be clinically effective against human colon cancers using a daily oral administration schedule.